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Exploring the potential of 3-nitrobenzaldehyde thiosemicarbazone: versatile ligand for coordination complexes and its multidisciplinary applications – a review

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ABSTRACT

3-Nitrobenzaldehyde thiosemicarbazone demonstrates a versatile nature in forming coordination complexes with various metals. These complexes have garnered significant interest in fields such as coordination chemistry, medicinal chemistry, catalysis, and material science. The ligand's nitrogen and sulfur atoms serve as potential coordination sites, allowing for the formation of diverse complexes with different metals. These complexes exhibit bioactive properties in medicinal chemistry, serve as catalysts in catalytic processes, and contribute to the development of novel materials with tailored functionalities in material science. The exploration of 3-nitrobenzaldehyde thiosemicarbazone complexes with multiple metals offers promising avenues for research and application in various scientific disciplines.

Keywords**:** 3-Nitrobenzaldehyde thiosemicarbazone, coordination complexes, metals, versatility, coordination chemistry, medicinal chemistry, catalysis

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1. INTRODUCTION

Thiosemicarbazones are known for their coordination ability, forming complexes with metal ions. The reactivity and coordination properties of 3-nitrobenzaldehyde thiosemicarbazone will depend on the specific metal ion and reaction conditions. Under normal conditions, thiosemicarbazones are generally stable compounds. 3-Nitrobenzaldehyde thiosemicarbazone is a yellow or light orange solid compound that belongs to the family of thiosemicarbazone ligands. It has a molecular formula of $C_9H_9N_5O_2S$ and a molecular weight of 243.27 g/mol. The compound's chemical structure consists of a benzaldehyde moiety attached to a thiosemicarbazone group, which contains a nitrogen-nitrogen double bond and a sulfur atom.

The melting point of 3-nitrobenzaldehyde thiosemicarbazone are in the range of 150-250 °C. It is sparingly soluble in water but dissolves in organic solvents like ethanol, methanol, chloroform, and dichloromethane. However, factors such as pH, temperature, and the presence of metal ions or oxidizing agents can influence their stability. Spectroscopic techniques such as infrared spectroscopy, nuclear magnetic resonance spectroscopy, and mass spectrometry can be used to characterize the compound and determine its structural features.

3-Nitrobenzaldehyde thiosemicarbazone is of significant interest due to its versatile nature and potential applications. It serves as a valuable ligand in coordination chemistry, enabling the synthesis of diverse coordination complexes. Additionally, its bioactive properties make it a promising candidate in medicinal chemistry for potential therapeutic applications. The thiosemicarbazone ligand has several potential coordination sites, including the nitrogen atoms and the sulfur atom. Due to their pharmacological properties [1, 2], including antibacterial, antiviral, antifungal, antitumor, antimalarial, trypanocidal, anti-inflammatory, and antiparasitic activities, thiosemicarbazone synthesis and chemical investigation of these compounds and their transition metal complexes are of great interest.

The adsorption studies involving complexes of 3-Nitrobenzaldehyde thiosemicarbazone can be employed in various applications such as wastewater treatment, environmental remediation, and purification processes. The metal ion typically coordinates with one or more of the nitrogen atoms and may also interact with the sulfur atom. The coordination bonds are formed through the donation of electron pairs from the ligand to the metal ion, resulting in the formation of a stable complex. The ability of 3-nitrobenzaldehyde thiosemicarbazone to form complexes with different metals is valuable for applications in fields such as coordination chemistry, medicinal chemistry, catalysis, and material science [3-7]. By varying the metal ion and ligand composition, researchers can tailor the properties and activities of the resulting complexes to suit specific applications and desired outcomes.

2. BIOLOGICAL POTENTIAL OF THE LIGAND

Meta nitro benzaldehyde thiosemicarbazones exhibit enhanced biological activity compared to their ortho or para counterparts due to several factors. The presence of the nitro group at the meta position affects the electronic properties of the molecule, making it more electron-withdrawing. This electron-withdrawing effect can contribute to increased antimicrobial, antifungal, or anticancer activity. Additionally, the spatial arrangement and molecular conformation resulting from the meta position of the nitro group may optimize the binding affinity and interactions with target biomolecules, thereby improving biological activity. The nitro group in the meta position can also undergo reduction reactions, generating reactive species that exhibit cytotoxic effects and interfere with cellular processes. Furthermore, the lipophilicity of the compound may be influenced by the presence of the nitro group in the meta position, affecting its bioavailability and ability to penetrate cellular membranes.

However, it is important to consider that the specific biological activity of meta-nitrobenzaldehyde thiosemicarbazones can vary depending on the target, cellular environment, overall molecular structure, metal coordination (if applicable), and experimental conditions. In this paper, the 3-nitrobenzaldehyde thiosemicarbazone ligand and its various properties are discussed.

3. MATERIALS AND METHODS

Thiosemicarbazone ligands are known to exhibit bidentate coordination behavior, typically binding to metal ions through the sulfur atom and one of the hydrazino nitrogen atoms. This bidentate coordination mode forms stable complexes with transition metal ions [8]. However, it is also possible for thiosemicarbazone ligands to coordinate to a metal ion solely through the sulfur atom, resulting in monodentate coordination. This coordination mode is less common but has been reported in certain transition metal complexes [9-11]. Thiosemicarbazone ligands can exhibit multidentate coordination if additional donor groups are present in the aldehyde or ketone moiety from which they are derived. This allows for the formation of complexes with higher coordination numbers [12]. The coordination of metal ions with thiosemicarbazones can enhance their biological activities, which has led to increased interest in studying and utilizing metal complexes with these ligands. Due to their diverse range of bonding and stereochemical modes and possible therapeutic benefits, thiosemicarbazones and related metal complexes are a significant focus of research in terms of their synthesis and structural studies [13-17].

The fact that biological activities are often increased upon complexation has sparked interest in metal complexes containing thiosemicarbazone and semicarbazone ligands. It's important to note that the behavior of thiosemicarbazone ligands and their coordination properties can vary depending on the specific ligand structure, metal ion, and surrounding conditions [18]. Meta nitro benzaldehyde thiosemicarbazone (mNB-TSC) is a type of ligand used in coordination chemistry. Ligands are molecules or ions that can donate electron pairs to a central metal atom or ion, forming a coordination complex. In the case of mNB-TSC, it serves as a bidentate ligand, meaning it can bind to a metal ion through two donor sites. The structure of mNB-TSC consists of a benzene ring substituted with a nitro group ($-NO_2$) at the meta position and a thiosemicarbazone functional group ($-C(NH-NH_2)-NH_2$) attached to the aldehyde group. The thiosemicarbazone moiety provides the donor sites for coordination to a metal ion. mNB-TSC and similar ligands are widely used in coordination chemistry for their ability to form stable complexes with various metal ions. These complexes can exhibit diverse properties and applications in fields such as catalysis, medicinal chemistry, and materials science.

A number of Cu(II), Ni(II), and Co(II) metal complexes with the general formula $[M(L)_2]Cl_2$ have been prepared by the author and characterised using elemental analysis, spectral (IR and 1H NMR) studies, molar conductance, magnetic susceptibility measurements, and thermogravimetric analysis [19]. The spectrum information points to the participation of azomethine nitrogen and thione sulphur in the coordination to the core metal ion. According to the investigations mentioned above, the square-planar geometry of the Cu(II) and Ni(II) complexes has been ascribed, respectively, whereas the cobalt(II) complex is tetrahedral in structure. Numerous bacteria have been investigated in vitro using the free ligand and its metal complexes. The substances that were examined showed a lot of action.

The study presents an abstract perspective on the research conducted on the synthesis, characterization, theoretical calculations, molecular docking, and cytotoxicity of complexes formed by nickel (II), palladium (II), and platinum (II) with SNO-group thiosemicarbazone and DMSO. Thiosemicarbazones containing an SNO-group have demonstrated potential biological activities, particularly cytotoxicity against cancer cells [20]. The synthesis process involved the reaction between metal salts and the thiosemicarbazone ligand in the presence of DMSO as a co-ligand. The resulting complexes were subjected to comprehensive characterization using spectroscopic, elemental, and thermal analysis techniques by the author.

To gain insights into the electronic structure and properties of the complexes, Density Functional Theory (DFT) calculations were performed. DFT, a computational approach based on quantum mechanics, allowed for the assessment of the molecular properties through theoretical simulations. Additionally, molecular docking studies were conducted to investigate the potential binding interactions between the complexes and target biomolecules. This analysis helps in understanding the possible mechanisms of action of the complexes in biological systems.

Thiosemicarbazones are organic compounds that contain a thiosemicarbazide functional group ($-CSNHNH_2$). In this study, the authors focused on the synthesis of copper (II) complexes with specific thiosemicarbazone ligands using microwave-assisted techniques [21]. Microwave irradiation is known to accelerate chemical reactions, leading to shorter reaction times and increased product yields.

The synthesis process in this paper involved the reaction between copper salts and the selected thiosemicarbazone ligands under microwave irradiation. The resulting complexes were then characterized using various analytical techniques, including spectroscopy (UV-Vis, FT-IR), elemental analysis, and magnetic susceptibility measurements. These characterization methods helped to determine the structural and physical properties of the synthesized complexes.

The article also highlights the biological activities of the copper (II) complexes. The authors investigated the cytotoxicity of the complexes against selected cancer cell lines, aiming to evaluate their potential as anticancer agents. Additionally, antimicrobial studies were conducted to assess the complexes' effectiveness against bacterial and fungal strains.

By employing microwave-assisted synthesis, this research provides a time-efficient and convenient method for the preparation of copper (II) complexes with thiosemicarbazone ligands. The characterization of these complexes aids in understanding their structure and properties. Furthermore, the evaluation of their biological activities offers insights into their potential applications in cancer therapy and antimicrobial treatments.

In the current study, the focus was on the synthesis and characterization of two thiosemicarbazone ligands, namely 4HAT (4-hydroxyacetophenone thiosemicarbazone) and 3NBT (3-nitrobenzaldehyde thiosemicarbazone). These ligands were reacted with Cobalt (II) metal to form novel complexes, specifically $[Co(L1)_2Cl_2]$ and $[Co(L2)_2Cl_2]$, where L1 represents 4HAT and L2 represents 3NBT [22]. To characterize the synthesized compounds, various analytical techniques were employed. FTIR spectroscopy was used to analyze the functional groups present in the compounds, while UV-visible spectral analysis provided insights into their electronic properties. Furthermore, the antibacterial activities of the ligands and their metal complexes were evaluated through in vitro testing against *Escherichia coli*, *Staphylococcus aureus*, and *Bacillus subtilis* bacteria. This assessment aimed to assess the potential of the synthesized compounds as antibacterial agents. The study involved the synthesis and characterization of two thiosemicarbazone ligands and their Cobalt(II) metal complexes by the researchers. The compounds were characterized using various techniques, and their antibacterial activities were assessed against selected bacterial strains. These findings contribute to understanding the potential applications of these compounds in combating bacterial infections.

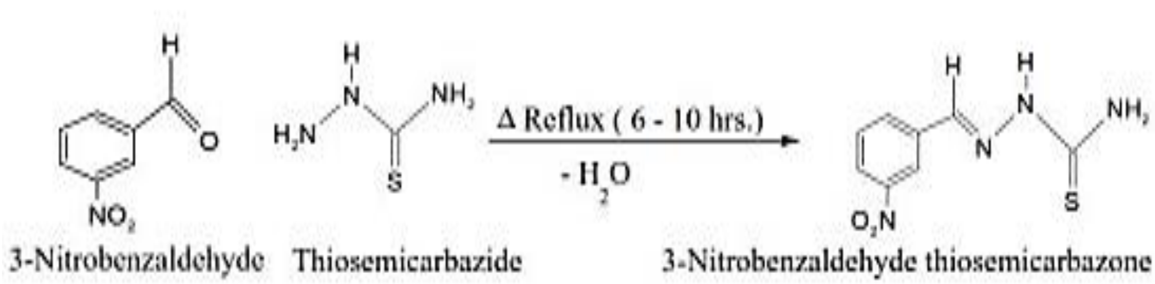


Figure 1. Synthesis of 3-nitrobenzealdhyde thiosemicarbazone

In this investigation, the 3-nitrobenzealdhyde thiosemicarbazone ligand and its transitional metal complexes with Nickel (II), Copper (II), and Cobalt (II) were synthesised, characterised, and tested for antibacterial and antifungal activity. FT-IR and UV techniques were used to characterise the synthesised molecules. The synthesis of the azomethine group (-C=N-H), lack of the carbonyl group (C=O), and creation of (M-N) and (M-S) bonds with all metal ions are confirmed by the findings of the FT-IR and UV spectra of the ligand and its metal complexes.

The silver nitrate test shows that the chloride ion was not within the range of coordination, and the findings suggest that the ligand is a neutral and bidentate species that coordinated with all three metal ions through azomethine N and thione S. The disc diffusion method was used to test the antimicrobial activity of the ligand and its metal complexes against four different bacterial species (Bacillus subtilis, Staphylococcus aureus (Gramme +ve), Escherichia coli, and Pseudomonas aeruginosa (Gramme -ve), as well as one fungus (Candida ablicans) at different concentrations (75 and 100 mg/ml). According to the findings, the Copper (II) complex and free ligand were ineffective against all varieties of bacteria and fungus, whereas the Nickel (II) and Cobalt (II) complexes displayed a variety of actions against four varieties of bacteria and fungi [23].

In this article, a 1:1 molar mixture of semicarbazide hydrochloride and 3-nitropenzaldehyde was condensed in an ethanolic medium to create the semicarbazone ligand. Using ethanol as a solvent, this ligand was employed to create metal complexes of copper (II) and nickel (II) in a 1:2 molar ratio.

Molar conductance, as well as UV and IR spectral investigations, have been used to examine the characterization and structural elucidation of produced metal complexes. The whole of the produced compounds had a crucial impact on both gram-positive (*Staphylococcus aurous*) and gram-negative (*Escherichia coli*) bacteria [24].

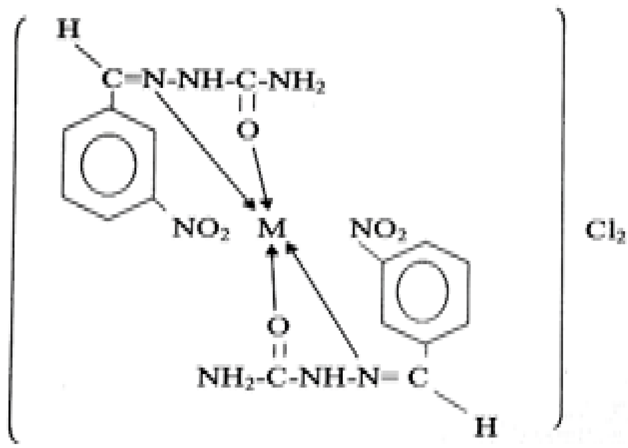


Figure 2. Proposed structures of the Cu (II), Ni (II) complexes

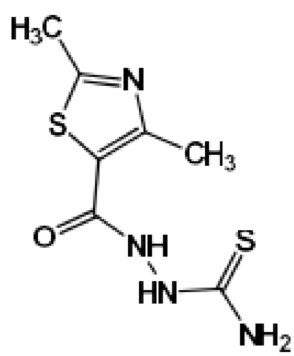
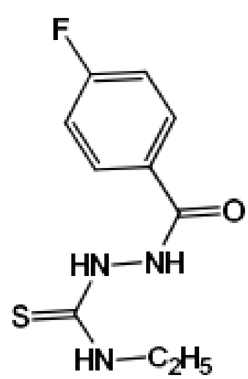
In contrast to the Na[NiL.OAc] complex, which is formed with the same ligand and CH_3COO, the [PdL.dmso] and [PtL.dmso] complexes of the ligand H2L with SNO sites and DMSO are square planar. The compounds were characterised by FTIR, UV-Vis, ^{1}H and ^{13}C NMR spectroscopy, micro and physical examination. Single crystal X-ray diffraction analysis was used to comprehensively clarify the structures of the [PdL.dmso] and [PtL.dmso] complexes [25]. Density functional theory (DFT) was used to calculate the ideal molecular geometries of compounds, as well as the HOMO-LUMO energies and other metrics, using the 6-311 G (d, p) and LANL2DZ basis sets. With an IC50 of 15.6 M and a selectivity index of 2.8 against Hela, the [PdL.dmso] demonstrated the greatest activity among all

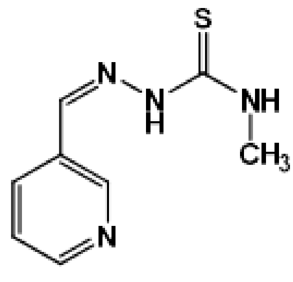
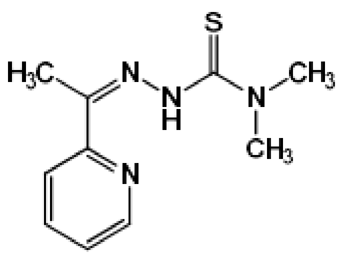
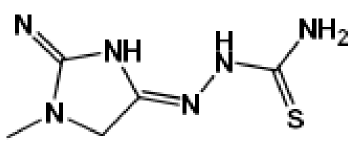
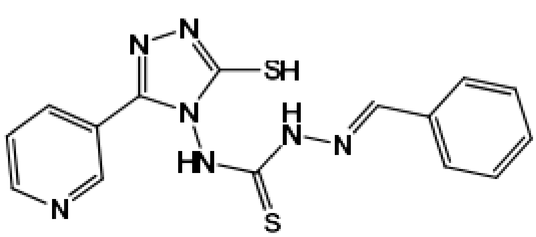
A new Ligand - metal complex was synthesised by the authors. Meta-nitro benzaldehyde thio semicarbazone (m-NBTS) complexes with metal [M= Cr (III) and Fe (III)] to form $[M (m\text{-}NBTS)(Py)_2Cl_2]Cl$, which have been characterized by elemental analysis, IR, UV-Visible, Conductivity measurement and Thermal studies. Elemental Analysis suggests 1:1:2 (M:NBTS:Pyridine) Stoichiometry for the complex. Electronic Spectra revealed the geometry to be Octahedral in nature [26].

The use of microwave irradiation to prepare Schiff base metal complexes has drawn more attention because of its excellent method for producing quick and stable products in higher yields while using less energy [27]. In addition to biological uses, they serve as a catalyst in Aldol processes and polymerization, chemical reactions, oxidation reactions, and other processes. The antibacterial, antifungal, and anticancer properties of several metal complexes generated from Schiff bases and synthesised utilising microwave techniques are described in this paper.

The Table 1 shows few complexes using the ligand Meta-nitro benzaldehyde thio semicarbazone.

Table 1. Few Metal complex involving the ligand meta-nitro benzaldehyde thio semicarbazone

Complex	Bioactivity	Literature
 1-(2,4-dimethyl thiazole-5-carboxyl)-N-4-ethyl-thiosemicarbazide	Antibacterial effects on *E. coli*	Mohammad Asifa, Saad Alghamdi, Chemical and Biological potentials of semicarbazide and thiosemicarbazide derivatives and their metals complexes, Advanced Journal of Chemistry, Section B, 2021, 3(3), 243-270, DOI: 10.22034/ajcb.2021.294269.1086
 1-(4-fluoro benzoyl)-N-4-ethyl thiosemicarbazide	Antibacterial effects on *E. coli*	
	Antibacterial effects on both *E. coli* and *S. aureus*	[28]. M. Sheikhy, A.R. Jalilian, A. Novinrooz, F. Motamedi-Sedeh. Synthesis and in vitro antibacterial evaluation of some thiosemicarbazides and thiosemicarbazones. J. Biomed. Sci. & Engineer., 5 (2012) 39-42.

 2-pyridine-aldehyde-4-N-methyl thiosemicarbazone		
 2-acetyl pyridine-4-N, N'-dimethylthio-semicarbazone	Antibacteria l effects on both *E. coli* and *S. aureus*	
 2-(2-imino-1- methylimidazolidin-4-ylidene)hydrazine carbothioamide	Antioxidant Activity	[29]. A. Ahmed, K. Yasmein, H. Heba, A. Ali. Antioxidant, anti-microbial and theoretical studies of the thiosemicarbzone derivative Schiff base. Org. Med. Chem. Lett., 2012, 2, 4.
 Phenyl derivatives of N-(5- mercapto-3-pyridyl-3-yl-4H-1,2,4-triazol-4-yl)-thiosemicarbazone	Antifungal activity	[30]. A. Kshirsagar, M.P. Toraskar, V.M. Kulkarni, S. Dhanashire, V. Kadam. Microwave assisted synthesis of potential anti infective and anticonvulsant thiosemicarbazones. Int. J. ChemTech Res., 1(2009), 696-701.

In this study, the authors focused on synthesizing zinc(II) complexes of (3-nitro-2-oxo-benzaldehyde thiosemicarbazonato) ligands and evaluating their antimicrobial activity against specific pathogens. The position of the nitro group in the phenyl ring was varied to investigate its impact on the activity. The researchers synthesized several zinc(II) complexes using different derivatives of the thiosemicarbazone ligand, where the nitro group was positioned at various locations in the phenyl ring. They characterized the complexes using various analytical techniques. The antimicrobial activity of these complexes was assessed against *Klebsiella pneumoniae*, *Salmonella typhimurium*, methicillin-resistant *Staphylococcus aureus* (MRSA), and *Candida albicans*. The researchers performed agar well diffusion and broth microdilution assays to determine the inhibitory effects of the complexes against these microorganisms. The results showed that the position of the nitro group in the phenyl ring of the ligand significantly influenced the antimicrobial activity of the zinc (II) complexes.

The complexes with the nitro group positioned at the meta position demonstrated the highest antimicrobial activity compared to those with the ortho or para positions. These findings highlight the importance of the position of functional groups in the ligand structure, as it can significantly affect the biological activity of the resulting metal complexes. The study provides insights into structure-activity relationships and suggests that modifications of the ligand framework can be explored to enhance the antimicrobial potential of thiosemicarbazone-based complexes.

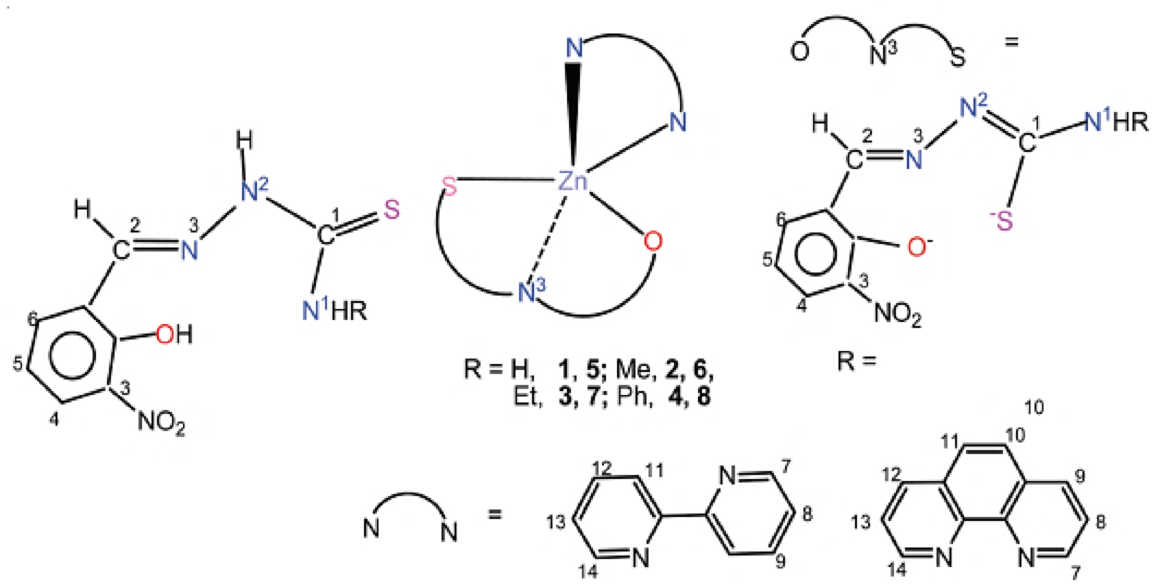


Figure 4. Zinc derivatives with the ligand

4. CONCLUSION

The future of 3-Nitrobenzaldehyde thiosemicarbazone and its coordination complexes seems bright. Further breakthroughs and applications in a variety of industries are expected as research progresses. Exploration of novel metal-ligand combinations and synthesis of complex structures offer enormous promise in coordination chemistry. The discovery of focused and effective therapeutic medicines based on 3-Nitrobenzaldehyde thiosemicarbazone complexes is envisaged in medicinal chemistry. Furthermore, using these complexes as catalysts in catalytic processes is predicted to increase reactivity and selectivity. These future directions will contribute to the development and use of 3-Nitrobenzaldehyde thiosemicarbazone and its coordination complexes as research advances, bringing up new avenues.

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